PILOT STUDY: UNIQUE RESPONSE OF BONE TISSUE DURING AN INVESTIGATION OF RADIO-ADAPTIVE EFFECTS IN MICE

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PURPOSE

We obtained bone tissue to evaluate the collateral effects of experiments designed to investigate molecular mechanisms of radio-adaptation in a mouse model. Radio-adaptation describes a process by which the prior exposure to low dose radiation can protect against the toxic effect of a subsequent high dose exposure.
In the radio-adaptation experiments, C57Bl/6 mice were exposed to either a Sham or a priming Low Dose (5 cGy) of Cs-137 gamma rays before being exposed to either a Sham or High Dose (6 Gy) 24 hours later.

ANALYSIS

Bone tissue were obtained from two experiments where mice were sacrificed at 3 days (n=3/group, 12 total) and at 14 days (n=6/group, 24 total) following high dose exposure. Tissues were analyzed to 1) evaluate a radio-adaptive response in bone tissue and 2) describe cellular and microstructural effects for two skeletal sites with different rates of bone turnover. One tibia and one lumbar vertebrae (LV2), collected at the 3-day time-point, were analyzed by bone histomorphometry and micro-CT to evaluate the cellular response and any evidence of microarchitectural impact. Likewise, tibia and LV2, collected at the 14-day time-point, were analyzed by micro-CT alone to evaluate resulting changes to bone structure and microarchitecture. The data were analyzed by 2-way ANOVA to evaluate the effects of the priming low dose radiation, of the high dose radiation, and of any interaction between the priming low and high doses of radiation. Bone histomorphometry was performed in the cancellous bone (aka trabecular bone) compartments of the proximal tibial metaphysis and of LV2.

RESULTS

Cellular Response @ 3 Days

The priming Low Dose radiation decreased osteoblast-covered bone perimeter in the proximal tibia and the total cell density in the bone marrow in the LV2. High Dose radiation, regardless of prior exposure to priming dose, dramatically reduced total cell density in bone marrow of both the long bone and vertebra. However, in the proximal tibia, High Dose radiation increased the osteoclast-covered bone perimeters, the density of adipocytes in bone marrow, and the area of bone marrow occupied by fat cells -- while in the LV2, adipocytes were rare and not stimulated by High Dose radiation. In an unexpected response, High Dose radiation dramatically increased (10-fold) osteoblast-covered bone perimeter in the LV2.

Bone Microarchitecture @ 3 Days

As expected for a study of short duration, there were relatively few changes in trabecular bone microarchitecture. The priming low dose of radiation resulted in a tendency for both bone area (B.Ar/T.Ar %) and trabecular thickness (Tb.Th) to be decreased in the proximal tibia; in the LV2, the priming low dose radiation resulted in an increase in Tb.Th. There was no interaction between the priming low dose and high dose radiation on indices of bone microarchitecture. High dose radiation, however, resulted in a significant decrease in trabecular number (Tb.N) and an increase in trabecular spacing (Tb.Sp) in the proximal tibia.

Bone Structure & Microarchitecture @ 14 Days

High Dose radiation resulted in shorter tibia in mice. There were no changes in measures of cortical bone parameters (cross-sectional volume, cortical bone volume, bone marrow volume, cortical thickness.) Priming Low Dose radiation had no independent effect on cortical (tibia) or cancellous (tibia and LV2) bone mass or architecture. There was no significant interaction between the priming dose and the high dose radiation exposures except for an effect (<0.049) on bone volume (BV/TV) in the proximal tibia. In contrast, High Dose radiation had profound effects on cancellous bone microarchitecture in both skeletal specimens: bone volume and trabecular number (Tb.N) were reduced and trabecular spacing was increased. Trabecular thickness was also increased. These observations indicate that there was a stimulation of both bone resorption and bone formation.

CONCLUSIONS:

Radiation has pronounced effects on cellular endpoints of bone tissue displaying increases in both osteoblast perimeter (LV2) and osteoclast perimeter (proximal tibia). Such observations suggest that High Dose radiation accelerates the turnover of bone leading to bone loss and a disruption of trabecular bone microarchitecture. Based upon parallel studies by the OSU co-investigators, the skeletal changes induced by lethal radiation are reversible.